

Serial No. 09/842.337

Remarks

Claims 1.11, and 12 are currently pending. Claims 1 and 11-12 stand rejected under 35 U.S.C. § 112, first paragraph.

At the outset, Applicants respectfully submit that the EMEA document supporting use of zymogen for purpura fulminans and coumarin-induced skin necrosis was not available for consideration due to clerical error without any intent to deceive. Likewise, due to clerical error without any intent to deceive, the previously submitted Gerson *et al.* reference (Gerson *et al.*, Pediatrics 91:418-422, 1993) was missing page 419. Accordingly, Applicants herewith submit the EMEA document and the complete Gerson *et al.* reference (Cites No. CL and CI, respectively, on the Form PTO 1449 submitted with the RCE application filed on October 14, 2003).

Applicants respectfully request reconsideration and allowance of claims 1, 11, and 12 in view of the following remarks.

Rejection of Claims 1, 11, and 12 under 35 U.S.C. § 112, First Paragraph

Claims 1, 11, and 12 stand rejected under 35 U.S.C. § 112, first paragraph for lack of enablement. The Examiner states that since there are no working examples of administering a pharmaceutically effective amount of human protein C zymogen to a patient, as set forth by the present invention, one must consider the state of the art. In doing so, the Examiner has relied on Bang *et al.* (U.S. 5,151,268) to conclude that it is not clear that therapeutic levels of aPC can be reached for any disease state, let alone the specific viral hemorrhagic fever treatment of the present invention. However, Applicants respectfully submit that nothing in Bang *et al.* supports an assertion that a slow conversion rate to activated protein C is equated with no efficacy.

Applicants further respectfully submit that protein C zymogen has been demonstrated to be efficacious, as shown by the Gerson *et al.*, Rivard *et al.* (Rivard *et al.*, J. Pediatr. 126:646-652, 1995), and Rintala *et al.* (Rintala *et al.*, Crit. Care Med. 26:965-968, 1998) references, which pre-date the priority date of the present application, as well as the de Kleijn *et al.* reference (de Kleijn *et al.*, Crit. Care Med. 31:1839-1847, 2003), which post-dates the priority date of the present application. Each of these references uses a commercially available protein C concentrate, that is, protein C zymogen. Applicants respectfully submit that the protein C concentrate described in these reference is not activated protein C (aPC), as asserted by the Examiner.

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For example, de Kleijn *et al.*, describes treatment of patients with protein C, not aPC, in the second paragraph, middle column page 1841 as follows:

Treatment. Patients were randomized to receive intravenous placebo (albumin human 1%) or 50 IU/kg, 100 IU/kg, or 150 IU/kg protein C concentrate Human Vapor Heated (Baxter AG, Vienna, Austria), referred to as PCConc, with equal probability. This PCConc contains only trace amounts of APC. (emphasis added).

Thus, de Kleijn *et al.* administered protein C zymogen, and not aPC. Likewise, each of the Gerson *et al.*, Rivard *et al.*, and Rintala *et al.* references used a similar preparation of protein C zymogen, and not aPC. Gerson describes therapy with protein C-concentrate at the paragraph bridging columns 1 and 2 at page 419:

Protein C-concentrate therapy (human plasma derived, hepatitis B surface antigen and human immunodeficiency virus type 1 antibody nonreactive, vapor-heated, purified by monoclonal antibody chromatography from a viral inactivated concentrate of factor IX complex [details on file with Immuno A.G., Vienna, Austria])....

Thus, Gerson *et al.* used a protein C concentrate that was prepared and provided by the same commercial supplier as the protein C concentrate described in the de Kleijn *et al.* reference. Rivard *et al.* (column 2, paragraph titled "Materials" on page 647) and Rintala *et al.* (column 3, last paragraph, page 965) also describe administration of Protein C Concentrate (Human) Vapor Heated supplied by Immuno A.G., Vienna Austria.

In addition to the use of human protein C zymogen in the above-cited and other case studies, Applicants previously submitted an abstract from the European Agency for the Evaluation of Medicinal Products (EMA) describing approval of the medicinal product CEPROTIN. In the third paragraph of that abstract, the active substance of CEPROTIN is described as "protein C concentrate." That paragraph further describes that "Protein C is converted by a thrombin/thrombomodulin-complex to activated protein C (APC) on the endothelial surface." Therefore, Applicants respectfully submit that CEPROTIN, which is produced by Baxter AG in Austria, contains protein C zymogen, and not aPC as implicated by the Examiner.

Applicants are claiming the use of the protein C zymogen to treat viral hemorrhagic fever. The specification discloses how to make protein C zymogen (see Preparation 1 at p. 10 of the specification) and relevant dose ranges for treating patients in the clinic at page 8, lines 13-23 of the specification. In view of this disclosure and the state of the art regarding therapeutic use of protein C zymogen at the priority date of the present application, Applicants respectfully submit that the enablement requirement has been satisfied.

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Accordingly, Applicants request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Conclusion

Having addressed all outstanding issues, Applicants respectfully request entry and consideration of the foregoing amendments and reconsideration and allowance of the case. To the extent the Examiner believes that it would facilitate allowance of the case, the Examiner is invited to telephone the undersigned at the number below.

Respectfully submitted.



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The European Agency for the Evaluation of Medicinal Products

CPMP/1383/01

**COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
EUROPEAN PUBLIC ASSESSMENT REPORT (EPAR)****CEPROTIN**

International Nonproprietary Name (INN): Human protein C

Abstract

On 16 July 2001, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product CEPROTIN, which contains Human protein C. This decision was based on the assessment report and on the favourable opinion adopted by the Committee for Proprietary Medicinal Products (CPMP) on 29 March 2001. The Marketing Authorisation Holder responsible for this medicinal product is Baxter AG, Austria.

The approved indication is for the treatment of purpura fulminans and coumarin-induced skin necrosis in patients with severe congenital protein C deficiency. Treatment with CEPROTIN should be initiated under the supervision of a physician experienced in substitution therapy with coagulation factors/inhibitors where monitoring of protein C activity is feasible. Detailed conditions for the use of this product are described in the Summary of Product Characteristics (SPC) which can be found in this EPAR and is available in all European Union official languages.

The active substance of CEPROTIN, protein C concentrate, is an antithrombotic agent (B01 AX). Protein C is a normal constituent of human blood, in particular, a vitamin K-dependent anticoagulant glycoprotein synthesised in the liver. Protein C is converted by a thrombin/thrombomodulin-complex to activated protein C (APC) on the endothelial surface. APC is a serine protease with potent anticoagulant effects. The PC pathway provides a natural mechanism to control the coagulation system and to prevent excessive clotting.

The benefit of CEPROTIN is its anticoagulant effect. Twelve courses of short term prophylaxis prior to surgery or invasive therapy and nine courses of long term prophylaxis were included in the efficacy analyses. The studies showed that CEPROTIN suggests a benefit in the treatment of purpura fulminans and coumarin induced skin necrosis in patients with severe congenital protein C deficiency.

Only limited data on undesirable effects are available as no prospective safety studies have been performed. Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, rash, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed infrequently. In the clinical trials performed, two mild allergic adverse experiences occurred. There are individual reports of the occurrence of fever, arrhythmia, bleeding and thrombosis during the course of the treatment. If the preparation is used in patients with severe congenital protein C deficiency, antibodies inhibiting protein C may develop.

The CPMP, on the basis of efficacy and safety data submitted, considered that CEPROTIN showed adequate evidence of efficacy for the approved indication, as well as a satisfactory risk/benefit profile and therefore recommended that the Marketing Authorisation should be granted.

The CPMP recommended that the Marketing Authorisation should be granted "under exceptional circumstances" because the indications for which the medicinal product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence/data on the efficacy of the medicinal product.

The Marketing Authorisation Holder will submit additional information from a prospective clinical study in patients with severe congenital protein C deficiency and will report to the CPMP on the monitoring of all treatment courses of this medicinal product. All additional studies will be carefully monitored and the results will be reviewed by the CPMP.

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EXPERIENCE AND REASON—Briefly Recorded

"In Medicine one must pay attention not to plausible theorizing but to experience and reason together. . . . I agree that theorizing is to be approved, provided that it is based on facts, and systematically makes its deductions from what is observed. . . . But conclusions drawn from unaided reason can hardly be serviceable; only those drawn from observed fact." Hippocrates: *Precepts*. (Short communications of factual material are published here. Comments and criticisms appear as letters to the Editor.)

Severe Acquired Protein C Deficiency in Purpura Fulminans Associated With Disseminated Intravascular Coagulation: Treatment With Protein C Concentrate

ABBREVIATIONS. PF, purpura fulminans; DIC, disseminated intravascular coagulation; FFP, fresh frozen plasma; APC, activated protein C; ATIII, antithrombin III.

Purpura fulminans (PF) defines an acute, often lethal syndrome of disseminated intravascular coagulation (DIC) with rapidly progressive hemorrhagic necrosis of the skin due to dermal vascular thrombosis.¹⁻⁷ It is indicative of a severe disturbance in hemostasis now recognized to involve the protein C system in many cases.^{1,2,5,8-12} Purpura fulminans is usually seen in three clinical settings: (1) in the newborn period as a manifestation of homozygous protein C deficiency, or rarely protein S deficiency^{13,14}; (2) in individuals with acute, severe viral or bacterial infection where an acquired deficiency in protein C activity is documented^{1-3,5-8,10,12,15}; and (3) as a rare, postinfectious syndrome with a history of an antecedent "preparatory disease," most commonly a viral or bacterial illness involving the skin (eg, varicella or scarlet fever), with the sudden development, during an otherwise unremarkable convalescence, of progressive purpura and necrosis.^{3-5,7,10,12} Less commonly, PF may be seen in cholestasis, warfarin-induced skin necrosis, antiphospholipid syndrome (lupus anticoagulant), and heparin-induced thrombocytopenia.⁵ Thrombohemorrhagic complications are usually limited to the skin, sparing other organ systems. Pathological specimens in PF reveal microvascular thrombosis involving the dermis with perivascular hemorrhage. Clinically, skin lesions are characterized by a progression from echymotic areas to circumscribed lesions of purplish-black skin containing hemorrhagic bullae, eventually culminating in gangrene.⁶ Recent investigations into the biology of the endothelium and the protein C system have focused attention on the role of cytokines, particu-

larly interleukin-1 and tumor necrosis factor, in thrombotic purpura.^{10,16-21} Current treatment for acquired PF is empiric, utilizing fresh frozen plasma (FFP), heparin, and platelets.^{3,4,10,19,22,23} Morbidity and mortality remain unacceptably high.

We describe a case of severe, acquired protein C deficiency in a 13-year-old boy with varicella and group A β -hemolytic streptococcal sepsis, PF, DIC, and septic shock. Standard therapy with FFP was able to provide 20% to 50% of normal protein C activity and required administration of massive fluid volumes which became unacceptable because of an overwhelming expansion of third space volume and acute renal failure. Infusion of protein C concentrate²⁴⁻²⁶ led to an increase in plasma protein C concentration without large extravascular fluid volume accumulation, perhaps contributing to the reversal of a life-threatening hypercoagulable state.

CASE HISTORY

The patient, a 13-year-old white boy with varicella, was transferred from another hospital to the Medical Center Hospital of Vermont with a history of persistent fever, a question of a septic arthritis of the right hip, and a progressive purpuric rash. The patient had been in his usual state of good health until 8 days before admission, when varicella developed. Three days later he fell onto his right hip while climbing the stairs at his home. He went to his local hospital's emergency department 4 days later with a fever of 104°F and marked right hip pain. Roentgenograms of the right hip were reportedly normal and the patient was discharged to home only to return later that day with more discomfort and a petechial rash on his lower extremities. Aspiration of the right hip revealed clear fluid and the patient was admitted for observation. The following morning progression of the rash was noted with some areas of confluent purpura and poor peripheral perfusion.

On admission to the Medical Center Hospital of Vermont the patient was obtunded and hypotensive (central pulses palpable), with cyanotic, cold, poorly perfused extremities and large areas of confluent purpuric lesions from the lower abdomen to the toes. Crusting and hemorrhagic varicella lesions were noted over the entire body. Scattered areas of skin necrosis and petechial lesions were also present. Soon after arrival the patient experienced a cardiopulmonary arrest requiring chest compressions, intubation, and mechanical ventilation. Initial resuscitation involved massive fluid and blood product support (30 U of FFP, 5 U of packed red blood cells, 12 U of platelets, and 8 L of crystalloid over the first 24 hours of hospitalization). Continuous heparin therapy (50 U/kg bolus and 20 U/kg per hour) was initiated immediately upon arrival and intravenous immunoglobulin was also used initially because of the possibility of a varicella-induced thrombocytopenia.²⁷

Initial laboratory evaluation revealed a hematocrit of 0.36 and a white blood cell count of $7.6 \times 10^9/L$ with 0.35 neutrophils, 0.31 band forms, 0.22 lymphocytes, and 0.12 monocytes. The platelet count was $35000 \times 10^9/L$. The prothrombin time was 21.3 seconds (normal range 11 to 13 seconds, mean of normal 12 seconds); the partial thromboplastin time was 88 (normal range 25 to 37 seconds, mean of normal 31 seconds). The fibrinogen level was 2.2 g/L, D-dimer 59200 ng/mL, protein C activity 0%²⁸ (reference

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range 80% to 154%), free protein S 17% (reference range 44% to 127%) and total protein S 63%²⁹ (reference range 57% to 148%), antithrombin III 50% (reference range 86% to 128%), factor VIII 49% (reference range 60% to 140%), and factor V 30% (reference range 60% to 140%). A diagnosis of PF with acquired protein C deficiency and DIC secondary to varicella with a possible superimposed bacterial sepsis was made.

Initial cardiovascular support with dopamine (maximum dose of 15 µg/kg per minute) was augmented with nitroprusside and dobutamine, with subsequent normalization of cardiac output and vascular resistance. These agents were gradually discontinued over the first four hospital days. Oliguric acute renal failure and massive anasarca (24 kg weight gain in the first 24 hours of hospitalization) required hemodialysis and ultrafiltration from hospital day 8 to 15. A large retroperitoneal hemorrhage developed on hospital day 3, with active bleeding continuing for approximately 48 hours before spontaneous resolution occurred. No major pulmonary or central nervous system complications were observed.

The patient's skin lesions rapidly progressed over the first hospital day and hemorrhagic bullae formation became evident. An attempt at a lumbar epidural sympathetic nerve block to enhance blood flow was unsuccessful because of anasarca.³⁰ Further progression of new purpuric lesions slowed by the third hospital day. However, full-thickness skin necrosis of the entire right leg with gangrene of the lateral three toes and full-thickness skin necrosis of major areas of the left leg soon became evident. Burn care was instituted initially to treat the areas of skin necrosis, and subsequently the patient underwent skin grafting of the lower extremities with amputation of the lateral three toes of the right foot.

While initial protein C replacement therapy with FFP infusion was able to provide protein C activity levels of 20% to 50% (Fig 1), our major concern was the clinical inability of the patient to tolerate the volume load necessary to maintain these levels. Another consideration, theoretical in nature, was whether or not a protein C level of 20% to 50% was sufficient to reverse the severe coagulopathy, given the patient's progressive deterioration. With the diagnosis of severe protein C deficiency in the setting of profound PF, DIC, and sepsis (blood cultures and right hip aspirate revealed group A β -hemolytic streptococci), administration of protein C concentrate was considered. Within 4 hours of admission, Food and Drug Administration emergency Investigational New Drug approval was obtained along with Institutional Review Board approval and parental consent. Protein C concentrate was made available by the manufacturer, Immuno A.G. of Austria, and by Dr Hans P. Schwarz of Immuno A.G., who provided expertise and guidance.

Protein C-concentrate therapy (human plasma derived, hepatitis B surface antigen and human immunodeficiency virus type 1 antibody nonreactive, vapor-heated, purified by monoclonal anti-

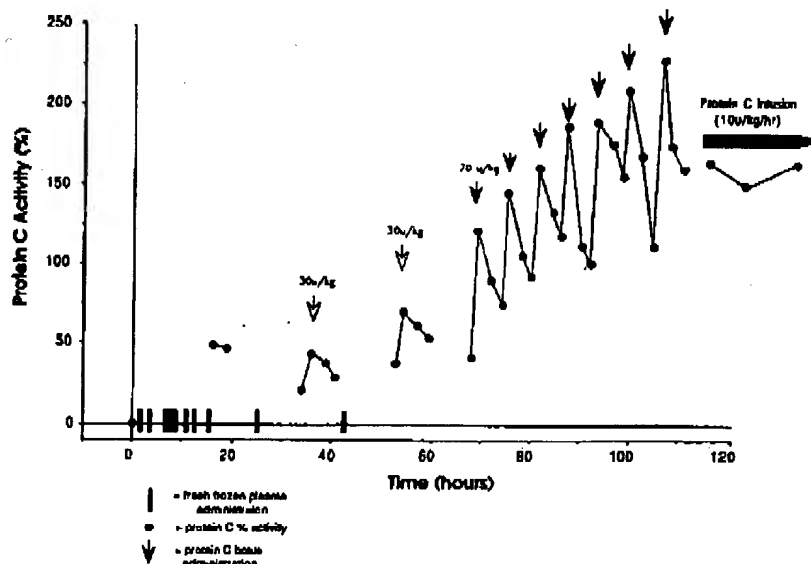
body affinity chromatography from a viral inactivated concentrate of factor IX complex [details on file with Immuno A.G., Vienna, Austria]) was begun within 36 hours of admission and was continued for 10 days. A test dose of 30 U/kg was given 36 hours after admission and repeated 18 hours later, resulting in protein C activity levels between 30% and 70% (Fig 1). When adequate supplies of the product were available, bolus therapy with 70 U/kg every 6 hours was begun. Subsequently, a continuous infusion of 10 U/kg per hour was used to maintain protein C activity at 100% to 200% (arbitrary goal being >100%) (Fig 1). Protein C infusion was continued for 11 days. D-Dimer levels on day 2, day 3, day 4, day 5, and day 21 were, respectively, 20 210 ng/mL, 35 790 ng/mL, 16 330 ng/mL, 8270 ng/mL, and 3280 ng/mL. These results demonstrate ongoing but resolving fibrinolysis documenting DIC. Levels of D-dimer have been reported to be inversely proportional to protein C activity in a neonate with homozygous protein C deficiency and purpura fulminans.³¹ In this particular report, the amount of protein C-concentrate therapy was adjusted to maintain a normal level of D-dimer.

The patient's parents had normal levels of protein C activity (father 98%, mother 81%), thus ruling out the possibility of the patient's having a hereditary protein C deficiency. No adverse reactions were noted during the period of therapy, and the patient's subsequent course revealed no adverse reactions attributable to the protein C concentrate. Four months after his initial hospitalization the patient was readmitted to the hospital with osteonecrosis of the right pelvis requiring debridement. At this time his protein C activity was 94%. The patient has returned to school and is ambulatory with crutches.

DISCUSSION

Protein C is a vitamin K-dependent zymogen of a serine protease which, after activation by thrombomodulin/thrombin complex on endothelial surfaces, exhibits antithrombotic properties and constitutes one of the major regulatory systems of hemostasis. Two mechanisms appear to define the anticoagulant properties of the protein C system: (1) activated protein C (APC) inactivates both the active form of factor VIII, the cofactor for factor IXa-induced factor X activation, and factor V, the cofactor for factor Xa-induced prothrombin activation, the two rate-limiting steps of the coagulation cascade; and (2) APC displays profibrinolytic properties perhaps by inhibiting plasminogen activator inhibitor. A neces-

Fig 1. Relationship between patient protein C levels and administration of protein C concentrate.



sary cofactor for these anticoagulant properties is another vitamin K-dependent protein, protein S.^{14,31-39} Thrombotic diatheses have been described with inherited and acquired deficiencies of either protein C or protein S. Additional hypercoagulable states have been associated with deficiencies of antithrombin III (ATIII), dysfibrinogenemia, and, less commonly, with disordered control of fibrinolysis.⁴⁰

Protein C plays a critical role in DIC.^{8,41-46} It is becoming increasingly clear that endothelial cells actively contribute to the maintenance and regulation of hemostatic balance, both in terms of anticoagulant and procoagulant function. The production of thrombin at the onset of DIC initiates both a procoagulant process involving the cleavage of fibrinogen and an anticoagulant effect consisting of the binding of excess thrombin to thrombomodulin on the endothelial surface with the subsequent production of APC. Activated protein C then inactivates factors Va and VIa in a classic negative feedback loop which slows the formation of excess thrombin and dampens the DIC process. Activated protein C itself is regulated by at least two major serine protease inhibitors, protein C inhibitor and α -1-antitrypsin, both of which inactivate APC by covalent binding to its active site.⁴³⁻⁵¹ Hemostatic balance can thus be returned to normal by the down-regulation of excess thrombin generation. The profibrinolytic effect of the protein C system can augment dissolution of excess thrombi. The consumption of protein C observed in our patient may have resulted from DIC-associated thrombin generation, transforming protein C to APC in the microcirculation. However, the unusually profound and selective depression of protein C levels could be due to an as yet poorly understood proteolytic process associated with either his bacterial and/or viral infection. Thus, the profound consumption of protein C, as demonstrated in our patient, probably led to a severe impairment of hemostatic regulation resulting in a marked propensity to develop thrombosis.

Recent human studies have supported this hypothesis by documenting a fall in protein C and protein S activity during DIC with a nadir at 12 to 24 hours after the onset,⁴¹ and the selective consumption of protein C (in comparison with ATIII and fi-

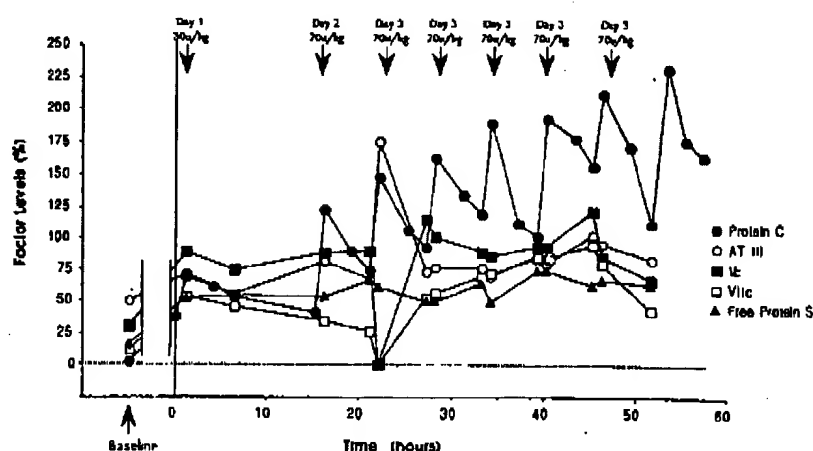
brinogen) in two patients with acquired PF and DIC with a return to normal levels after 4 to 7 days.⁹ Protein C activity has been measured in 85 patients who had DIC with or without purpura fulminans, and a range of values from undetectable to normal was noted although the majority had absent or decreased activity.^{8,15,41,45,46} Animal studies have shown that APC can protect baboons from the lethal coagulopathy associated with *Escherichia coli* infusion,⁵² while APC has also been shown to be profibrinolytic in a dog model.⁵³ Furthermore, APC inhibits platelet-dependent arterial thrombosis in a baboon model⁵³ and venous thrombosis in a dog model.⁵⁴

Provision of protein C concentrate during the early stages of DIC could help maintain the necessary regulatory control of the protein C system, thereby arresting the DIC process.^{8,41,55} The protein C and free protein S levels in our patient are shown in Fig 2 beginning with the second 30 U/kg infusion, as shown in Fig 1, along with the levels of ATIII and factors V and VII. The single observation of very low levels of factors V and VII at 22 hours (Fig 2) remains unexplained. During the period that protein C activity was at its lowest, the clinical signs of PF were progressing the most rapidly. The mild to moderate decrease in free protein S, ATIII, and factors V and VII and the normal levels of fibrinogen compared to the profound reduction in protein C activity suggest a possible selective consumption and/or selective decrease in production of this protein.

The use of protein C concentrate has been reported three times: in a patient with metastatic prostate cancer and DIC,²⁴ in an infant with homozygous protein C deficiency and PF,²⁵ and in a pregnant woman with protein C deficiency and thrombosis.²⁶ No side effects attributed to protein C-concentrate infusion were noted in any of these reports. In one study,²⁵ a biphasic half-life of protein C concentrate was determined to be 6 and 11 hours.

The dramatic presentation of a patient, usually a child, with PF and DIC, while uncommon, has long been a clinical enigma. Discussion of presumed pathogenesis is as varied as its therapy. Recently, it has become clear that PF occurs in individuals with

Fig 2. Coagulation factor levels during protein C infusions. AT, antithrombin.



inherited or acquired deficiencies in the protein C anticoagulation pathway. Major improvements in our understanding of hemostasis have led to more rational therapy. The present case describes a new mode of therapy and emphasizes the importance of the clinical recognition of PF and the laboratory diagnosis of the specific deficiency in the protein C pathway.

We have described the use of a newly available protein C concentrate in the treatment of a 13-year-old boy with varicella and bacterial sepsis, PF, DIC, and severe acquired protein C deficiency. The use of protein C concentrate is believed to have been instrumental in his survival. However, since PF may resolve without such therapy, our assumption is certainly not conclusive. We believe that all pediatric patients with PF should be evaluated for protein C deficiency. If protein C deficiency is demonstrated, protein C replacement therapy should be begun immediately. While it is not known to what level protein C activity should be raised in order to provide effective therapy, we arbitrarily chose to raise our patient's level to greater than 100% activity (normal, 80% to 154%). Because it is difficult to achieve even a level of 20% to 50% protein C activity with FFP when one considers the fluid limitations necessary in critically ill pediatric patients, who often have multiorgan system involvement, the use of protein C concentrate may offer the potential of a significant advance in the therapy of PF and DIC when associated with protein C deficiency.

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ABSTRACT

Sullivan PB, et al. The treatment of persistent diarrhea and malnutrition: long-term effects of in-patient rehabilitation. *Acta Paediatr Scand.* 1991;80:1025.

The association of diarrhea and malnutrition requires prevention and treatment of both entities to circumvent morbidity and mortality. However, once persistent diarrhea develops, nutritional rehabilitation is the primary mode of treatment. Although numerous studies have documented the initial efficacy of nutritional management, few long-term outcome studies are available. This study demonstrates failure to achieve complete recovery at one year in a cohort of children who responded well to initial in-patient nutritional therapy for persistent diarrhea and malnutrition (PDM).

Twenty-two Gambian children (10:12 male/female; mean age 18.9 months) with a mean duration of diarrhea of 12 weeks and suffering from Protein Energy Malnutrition (PEM) were treated aggressively as in-patients for malnutrition and any other concurrent illnesses (malaria, stress sepsis, UTI, otitis media, pneumonia, and oral candidiasis). Criteria for discontinuation of treatment was steady weight gain and cessation of diarrhea for five consecutive days. Steady improvement in weight for height, weight for age, mid-upper arm circumference, and immunologic status was documented during inpatient therapy. However, one year after the initial admission, 32% (F/22) were suffering from persistent/intermittent diarrhea with half of these children again demonstrating severe malnutrition.

The authors comment in the discussion section that PDM "is likely to recur when the child is discharged to an environment characterized by poor sanitation and inadequate water and food." Further prospective studies are necessary to determine the minimum period of supervised feeding needed to allow the weight gain necessary for normal linear growth; and the appropriate amount of zinc supplementation.

Submitted by Jeffrey Goldhagen, MD